REMARKS

Amendments

The claims have been amended to remove multiple dependencies. Additionally, claim 5 has been amended to clarify that the defined solvents are all the solvents used in the method. Claims 10 and 11 have been cancelled to expedite prosecution.

Claim Rejections – 35 USC §103

Claims 1-9 are pending in the application.

Claims 1-11 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Bhagwatwar et al (US 2003/0049320) in view of Yeh et al (U.S. 5,869,103).

The present invention relates to a method for the preparation of nano- or microparticles containing an active substance embedded in a polymer matrix. This method is a two-step process, comprising a first step of precipitating an active substance to provide a suspension of these particles of active substance in a solution that comprises a polymer dissolved in an organic solvent. This is step a) of claim 1. The thus obtained suspension is mixed with an aqueous surfactant solution, and the polymer is solidified to obtain a suspension of nano- or microparticles that contain an active substance. This is step b) of claim 1. In other words, the material formed by the claimed method is a suspension of nano- or micro- particles that themselves comprise particles of active substance. Because the physical parameters of the resulting particles, such as particle size, can be changed by processing conditions rather than by equipment changes, the performance characteristics of the final product can be changed "on the fly" during ongoing manufacturing processes to provide small batches of specialized product. See page 12, lines 13-27. Additionally, this in-situ precipitation of active agent can provide a product that has physical properties that are different from the properties of like compositions made by a different process. Specifically, the present method advantageously provides particles of the active substance that are very homogeneous in their appearance and show a narrow particle size distribution. See page 12, lines 28-30. This physical feature of the particles provides better control of release of the active substance in use of the final product. Finally, the process of the present invention advantageously may be used to encapsulate materials that are sensitive to shear forces, because the present process helps to avoid the negative

influence of physical stress factors (e.g. shear forces) on such active agents. See instant page 3, lines 15-20. These superior properties are afforded by a simple in-situ process that reduces the number of separate preparatory handling steps in the formation of the ultimate microparticles.

Bhagwatwar describes formation of a controlled release microcarrier delivery system wherein a gelled polymer droplet-in-oil dispersion is placed into a body in a semisolid form and cures to form the delivery system in-situ. This dispersion is formed by (i) dissolving a polymer in a biocompatible solvent at an elevated temperature to form a polymer solution, (ii) preparing a second oil phase solution of a biocompatible oil and a biocompatible emulsifier at an elevated temperature, (iii) mixing the polymer solution with the oil phase solution at an elevated temperature and (iv) subsequently cooling to refrigeration temperature. The microcarrier delivery system is produced in-situ by placing the gelled dispersion within a body. See the Abstract. The addition of the bioactive agent (also called a "drug") to the polymer system is discussed at paragraph [0079] of the specification. As noted therein, the drug is added to the polymer solution either as a solution or a suspension. The drug may or may not be soluble in the solvent of the polymer solution, but in either case the polymer is made to solidify and entrap or encase the drug within the solid matrix. Thus, the drug is taught to be in the physical state of being either in a solution or suspension when added to the polymer, and is either expected to stay in that state or to be solvated by the solvent of the polymer system. Bhagwatwar does not contemplate precipitation of the drug in the polymer solution prior to solidifying the polymer, as is required in the present claims. The benefits of the presently claimed in-situ precipitation of the active ingredient as discussed above therefore cannot be achieved.

Yeh describes microparticles including a mixture of a biodegradable polymer, a water soluble polymer, and an active agent. Preferred biodegradable polymers include lactide homopolymers or copolymers of lactide and glycolide. See the Abstract. Yeh is cited for its disclosure that microparticles comprising poly-DL-lactide-co-glycolide have been made in size ranges that are less than 1 micrometer. However, as in Bhagwatwar, the active agent of Yeh is provided in a solution, emulsion or suspension that is mixed with the polymer solution. A third solvent is mixed with this solution to precipitate the polymer and form the microspheres. See column 4, lines 35-50. Thus, there is no teaching or

suggestion of precipitation of the active agent in the polymer solution prior to solidifying the polymer, as is required in the present claims.

It is respectfully submitted that the references, either alone or in combination, fail to make obvious the present method and product by process as claimed. More specifically, neither reference teaches or suggests precipitation of the active agent in the polymer solution prior to solidifying the polymer, as is required in the present claims. The presently claimed unique process provides excellent flexibility in manufacturing capabilities, and additionally results in a product that can exhibit highly beneficial properties of active substance particles that are very homogeneous in their appearance and exhibit a narrow particle size distribution.

The subject matter of claim 2 is particularly unique and worthy of patent protection. This claim in particular provides a unique method of in situ precipitation of the active substance by selection of the solvent system to preferentially precipitate the active substance prior to solidifying the polymer. In this embodiment of the present invention, the first solvent L1 is a good solvent for the active substance and for the polymer, and the second solvent L2 is a good solvent for the polymer but a non-solvent for the active substance. By increasing the amount of L2 in the solution containing both the active substance and the polymer, the active substance is caused to precipitate. This preferred embodiment is discussed in detail at page 3, line 27 to page 4, line 8. This technique is clearly not taught or suggested by either reference or by both references in combination. The skilled artisan would have had no motivation for first precipitating the active substance in the presence of the polymer, and especially would have had no motivation for using a mixed solvent system as defined by the claims to effect the precipitation of the active substance.

Claim Rejections – 35 USC §112

Claims 1-11 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office Action states that the claims lack clarity in the use of solutions/solvents. This objection is respectfully traversed, because it is submitted that the terms are used in their prior art recognized meaning and consistently throughout the specification.

A solution is defined as "a homogeneous mixture of two or more substances, which may be solids, liquids, gases, or a combination of these" by the American Heritage Dictionary.

In claim 1, a solution is described that comprises a polymer that is dissolved in a solvent, and which additionally contains a suspension of the active substance. Thus, the term "solution" relates to the mixture, and "solvent" relates to a liquid component of the mixture. This first solution is mixed with an aqueous surfactant solution.

Claim 2 relates to the manipulation of components of the solution to achieve the precipitation of active substance in step a) of claim 1. The described manipulation provides that two different solvents (i.e. liquid components of the solution of claim 1) are added in described relative amounts in order to accomplish precipitation of the active substance.

Thus, it is submitted that the relationship between "solution" and "solvent" is consistent and clear, and would be readily understood by the skilled artisan.

Claim 5 defines that any organic solvents in the solution of claim 1 are partially soluble in water. This claim properly describes the organic solvent in both singular and plural forms, because claim 1 is drafted using open language "comprises" that permits the use of more than one organic solvent in the solution. In an abundance of caution, the expression "in the method" has been added to the claim so that there is no question that that the recited organic solvents are clearly all of the solvents in the system.

The Office Action further states that the claims are unclear as to what solutions/solvents are to be used in the active substance versus the polymer substance components. It is respectfully submitted that the scope of the claim is clear on consideration of the claims and the present specification.

The present invention provides in its broadest sense a new method of providing an active substance in a polymer matrix, whereby the polymer is dissolved in a solvent to form a solution, and an active substance is precipitated in that solution prior to solidifying the polymer. This precipitation can be carried out in any manner as will be appreciated by the skilled artisan. One technique that comes immediately to mind is by "salting out" the active substance by addition of salt ions. The skilled artisan readily understands the ability to select a solvent system based on this precipitation technique.

A preferred method that is discussed at length in the present specification is the use of a plurality of solvents, the first (to be used in the active substance component) being a good solvent for the active substance and the second (to be used in the polymer component) being a good solvent for the polymer but a non-solvent for the active substance. By increasing the amount of the second solvent in the solution containing both the active substance and the polymer, the active substance is caused to precipitate. This preferred embodiment is discussed in detail at page 3, line 27 to page 4, line 8.

Thus, it is respectfully submitted that in the broadest aspect of the present invention, any solvent may indeed be incorporated in a manner that will be readily understood by the skilled artisan. Further, the selection of the solvents for the preferred embodiments will also be readily understood by the skilled artisan in view of the teachings of the present specification. The skilled artisan can readily determine whether they infringe the present claims simply by determining if they carry out method including effecting precipitation of an active substance in a solution which comprises a polymer dissolved in an organic solvent to obtain a suspension of the active substance, and mixing the obtained suspension with an aqueous surfactant solution and solidifying the polymer to obtain a suspension of nano- or microparticles which contain an active substance.

Claim Objections

Claims 4-11 have been objected to under 37 CFR 1.75(c) as being in improper form because multiple dependent claim may not be depended therefrom.

The claims have been amended to remove multiple dependencies.

Conclusion

In view of the above amendments and remarks, it is respectfully submitted that the foregoing is fully responsive to the outstanding Office Action. Examination of all claims together, and early favorable consideration and passage of the above application to issue is earnestly solicited. In the event that a phone conference between the Examiner and the Applicant's undersigned attorney would help resolve any issues in the application, the Examiner is invited to contact said attorney at (651) 275-9811.

Respectfully Submitted,

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By: _____

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